REMARKS

Claims 1-5 are pending in this application. Claims 1-2 and 4-5 are amended herein for clarity to more particularly define the invention. Support for these claim amendments is found throughout the specification (e.g., on page 15, lines 8-11; on page 22, line 7 and in the Example section on pages 19-22) and in the language of the original claims, as set forth below. New claim 17 is added herein and support for this new claim can be found throughout the specification (e.g., Examples section on pages 19-22 and page 16, line 14 through page 17, line 14) and in the language of the original claims. It is believed that no new matter is added by these amendments and new claim and their entry and consideration are respectfully requested. In light of these amendments, new claim and the following remarks, applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

I. Recordation of Interview Summary

Applicants wish to make of record the Interview Summary mailed to applicants by Examiner Sitton on October 3, 2007. Applicants concur that this Interview Summary accurately reflects the substance of the personal interview on September 25, 2007, in which Supervisory Examiner Ram Shukla, Examiner Jehanne Sitton and applicants' representative, Dr. Mary Miller, participated. Applicants appreciate the opportunity to discuss this application and pending claims with the Examiners.

II. Rejection under 35 U.S.C. § 112, first paragraph (enablement)

The Office Acton states that claims 1-5 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Specifically, the Examiner provides an analysis of claims 1-5 pursuant to the factors set forth in *In re Wands*. These factors are 1) the quantity of experimentation necessary, 2) the amount of direction or guidance presented; 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims.

Applicants respectfully traverse this rejection and provide their own analysis of the claimed

invention pursuant to the factors set forth in *In re Wands*, demonstrating that the present invention is indeed enabled.

As an initial point, applicants respectfully point out that it is well established that the test for enablement is whether one skilled in the art could reproduce the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). The key word is "undue," not "experimentation," and "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.*, 8 USPQ2d at 1404 (quoting *In re Jackson*, 217 USPQ 804, 807 (CCPA 1982)). In *Wands*, claims to antibodies that required a screening procedure to isolate the desired hybridoma cells from enormous numbers of other cells present in the reaction mixture were held to not require experimentation that was "undue." *Id.*, 8 USPQ2d at 1406. The amount of effort required to make the antibodies was "not excessive." *Id.*, 8 USPQ2d at 1407. Thus, the test of enablement under 35 USC §112, first paragraph, is not whether any experimentation is necessary but rather is whether one skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation. *See,* MPEP 2164.01. Further, it is well settled that "a patent need not teach, and preferably omits, what is well known in the art" *Id.* In addition, in order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *See* MPEP 2164.04. It is also specifically noted that a specification which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the claimed subject matter must be taken as in compliance with the enablement requirement unless there is a reason to doubt the objective truth of the statements contained therein.

In an analysis of the factors of *In re Wands* regarding the nature of the invention and the breadth of the claims, the Office Action provides a summary of the subject matter of claims 1-5 as pending at the time of the Action, concluding that the claims require "...a predictive association between any single nucleotide polymorphism in the VKOR gene (VKORC1) and warfarin

sensitivity, in any human subject (claims 1-3) or in a single subject (claims 4-5). The Examiner then cites *Mycogen Plant Sci., Inc. v. Monsanto Co.* (243 F.3d 1316 1330 (Federal Circuit 2001)) to support her determination that the invention is in a class of inventions that the CAFC has characterized as "the unpredictable arts such as chemistry and biology."

In response to the Examiner's comment regarding "the unpredictable arts," applicants point out that although the biological sciences have been categorized as "unpredictable," the courts have long and repeatedly emphasized that the issue is not predictability *per se*, but the type of work and experimentation acceptable in the particular field, or fields, of the invention. For example, in *In re Angstadt,* the Court of Customs and Patent Appeals cautioned that:

> "If [our prior decision stands] for the proposition that the disclosure must provide "guidance which will enable one skilled in the art to determine, *with reasonable certainty before performing the reaction,* whether the claimed product will be obtained,.... then *all* 'experimentation' is 'undue', since the term 'experimentation' implies that the success of the particular activity is *uncertain*. Such a proposition is contrary to the basic policy of the patent act...."

In re Angstadt, 537 F. 2d 498, 503, 190 USPQ 214, 218-219 (CCPA 1976).

The court in *Angstadt* went on to emphasize that "...the key word is 'undue,' not 'experimentation'." *Id* at 504, 190 USPQ at 219. Thus, it is clear that even in an "unpredictable" art, an invention can be enabled, provided that the amount of experimentation required to carry out the invention is not undue.

Applicants respectfully point out that the claims are directed specifically to 1) human subjects, 2) a defined phenotype of increased sensitivity specifically to the drug, warfarin, and 3) a defined genotype of a SNP of the VKOR gene that is correlated with the defined phenotype according to well known and standard statistical methods. The invention as claimed is therefore quite specific in scope and definition and is not overly broad or unclear and it is apparent that the nature of the invention and breadth of the claims are such that one of ordinary skill in the art could

carry out the methods as claimed herein without undue experimentation and thus, both of these factors weigh in favor of the applicants. Indeed, it is applicants' own work that showed the identification of the VKOR gene and the association of SNPs in this gene with increased sensitivity to warfarin.

In her analysis of the pending claims pursuant to the *Wands* factors regarding the amount of direction or guidance and presence or absence of working examples, the Examiner points out 1) that the specification defines a subject with "increased sensitivity to warfarin" on page 15; 2) that the specification teaches three mutations identified in the VKOR gene that were examined for a correlation between their presence in a subject and the subject's maintenance dose of warfarin; and 3) that the claims broadly encompass the association between warfarin sensitivity by analyzing any SNP in the VKOR gene. The Examiner then states that 1) the specification is silent with regard to analyzing whether such associations were found across different races or ethnicities of human subjects; 2) the specification is silent as to an association of the over 25 particular SNPs in the VKOR gene as described in Geisen et al.; and 3) the specification provides no correlation between the identity of broadly any SNPs, that is their structure, with the function or phenotype of warfarin sensitivity, although, according to the Examiner, the claims broadly encompass the investigation of a broad scope of possible genomic regions for alleles that are indicative of warfarin sensitivity.

Applicants respectfully point out that claim 1 recites a method of identifying a human subject having an increased sensitivity to warfarin, wherein a therapeutic dose of warfarin for the subject is lower than a therapeutic dose of warfarin for a normal subject, comprising detecting in the subject the presence of a single nucleotide polymorphism in the VKOR gene, wherein the single nucleotide polymorphism is correlated with increased sensitivity to warfarin, thereby identifying the subject having increased sensitivity to warfarin. With such teaching, one of skill in the art would readily recognize that this method can be carried out in human subjects of any race or ethnicity and is based on having the knowledge of which SNPs of the VKOR gene are correlated with increased sensitivity to warfarin, which knowledge is or would be accessible to the ordinary artisan without undue experimentation. As the Examiner herself notes, the specification provides working

examples with actual reduction to practice of the methods of claims 1-5 and provides more than ample guidance for one of ordinary skill to identify and correlate any SNP in the VKOR gene without undue experimentation. It is not necessary that the specification teach each and every SNP and whether it is correlated with increased sensitivity to SNP for one of ordinary skill to carry out the methods of this invention. Single nucleotide polymorphisms are well known in the art and are readily identified in any particular gene one chooses to analyze. Determining warfarin dosages is well known and established in the art and correlating SNPs with particular phenotypic traits is routine, with the teachings of the specification, including the teaching of the VKOR gene sequence and the exemplary SNP analyses. Thus, similar to the holding of the court in *In re Wands*, "...all of the methods needed to practice the invention were well known." *Id.*, 8 USPQ2d at 1406.

To expound on the applicants' point that correlating SNPs with particular phenotypic traits is well known, applicants also provide the following list of publications (all of which have been made of record in the present application) which, in addition to those cited by the Examiner in the present Action (i.e., Rieder et al., Oldenberg et al., Rost et al.), provide more than ample evidence that such correlation methods as claimed herein were well known at the time of the applicants' invention and indeed were routine, particularly for correlating SNPs in the VKOR gene with warfarin sensitivity, pursuant to applicants' discovery that SNPs in the VKOR gene could be correlated with warfarin sensitivity. These publications evidence the fact that once applicants identified the VKOR sequence, disclosed it as such and correlated changes as minor as a SNP with warfarin sensitivity, numerous other groups were able to find and report other SNPs associated with warfarin sensitivity.

1) Li et al. "Polymorphisms in the VKORC1 gene are strongly associated with warfarin dosage requirements in patients receiving anticoagulation" *J. Med. Genet.* Online Publication April 12, 2006.

2) Montes et al. "The c.-1639G>A polymorphism of the VKORC1 gene is a major determinant of the response to acenocoumarol in anticoagulated patients" *Br. J. Haematol.* 133(2):183-187 (2006).

3) Wang et al. "VKORC1 Haplotypes Are Associated With Arterial Vascular Diseases (Stroke, Coronary Heart Disease, and Aortic Dissection)" *Circulation* 113(12):1615-1621, published on-line

March 20, 2006.

4) Vecsler et al. "Combined genetic profiles of components and regulators of the vitamin K-dependent gamma-carboxylation system affect individual sensitivity to warfarin" *Thromb. Haemost.* 95:205-211 (2006).

5) Mushiroda et al. "Association of VKORC1 and CYP2C9 polymorphisms with warfarin dose requirements in Japanese patients" *J. Hum. Genet.* 51(3):249-253 (2006).

6) Geisen et al. "VKORC1 haplotypes and their impact on the inter-individual and inter-ethnical variability of oral anticoagulation" *Blood* 94(4):773-779 (2005).

7) Quteineh et al. "Vitamin K epoxide reductase (VKORC1) genetic polymorphism is associated to oral anticoagulant overdose" *Thromb. Haemost.* 94(3):690-691 (2005).

8) Reitsma et al. "A C1173T Dimorphism in the VKORC1 Gene Determines Coumarin Sensitivity and Bleeding Risk" *PloS Medicine* 2(10):e312, published on-line October 11, 2005.

9) Veenstra et al. "Association of Vitamin K epoxide reductase complex 1 (VKORC1) variants with warfarin dose in a Hong Kong Chinese patent population" *Pharmacogenetics and Genomics* 15(10):687-691 (2005).

10) Sconce et al. "The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen" *Blood* 106(7):2329-2333 (2005).

11) Rieder et al. "Effect of VKORC1 Haplotypes on Transcriptional Regulation and Warfarin Dose" *N Engl J Med* 352(22):2285-2293 (2005).

12) Yuan et al. "A novel functional VKORC1 promoter polymorphism is associated with inter-individual and inter-ethnic differences in warfarin sensitivity" *Human Molecular Genetics* 14(13):1745-1751 (2005).

13) Wadelius et al. "Common VKORC1 and GGCX polymorphisms associated with warfarin dose" *The Pharmacogenomics Journal* 5(4):262-270 (2005).

14) Bodin et al. "Cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase (VKORC1) genotypes as determinants of acenocoumarol sensitivity" *Blood* 106(1):135-140 (2005).

15) D'Andrea et al. "A polymorphism in the VKORC1 gene is associated with an interindividual variability in the dose-anticoagulant effect of warfarin" *Blood* 106(1):645-649

(2005).

For at least the reasons provided above, applicants have demonstrated that the *Wands* factors regarding the amount of guidance, available not only in the present specification but also in the art, as well as the presence of working examples of the claimed invention, weigh in the applicants' favor.

As one final point in the analysis of these factors, the applicants note that the Office Action states that claims 4 and 5 encompass methods where correlations to warfarin sensitivity are made by analyzing a single subject and that in such a situation, the presence of a particular allele of a SNP in the VKOR gene and warfarin sensitivity could not be predictably established as it would not be known if the presence of the allele were due to chance or was actually associated with warfarin sensitivity.

Applicants appreciate the Examiner's comments on these claims, but note that it would be reasonable to expect that one of ordinary skill in the art would recognize that the methods of claims 4 and 5 are directed to correlating SNPs of the VKOR gene with warfarin sensitivity in a multiplicity or population of subjects. This is supported in the specification in the Example section, where it is clear that multiple subjects were analyzed both for warfarin sensitivity and the presence of SNPs in the VKOR gene, as well as on page 5, lines 33-34 of the specification, where the terms "a," "an" and "the" are defined to be singular or plural. However, in the interest of expediting prosecution of the pending claims to issue, claims 4 and 5 are amended herein to clarify this point.

The Office Action next comments on the *Wands* factors regarding the state of the art and predictability or unpredictability of the art. It is the Examiner's view that the unpredictability in the technology associated with the present invention is high and that although there is a large body of knowledge in the prior art related to polymorphisms in general and their association with diseases or disease states, the Examiner contends that the art is highly unpredictable with regard to functionality of polymorphism sites in genomic DNA.

As noted above, even in arts defined to be "unpredictable," the standard for enablement is still whether undue experimentation would be required to carry out the invention as claimed. As the applicants, as well as those following in their footsteps, have amply demonstrated, not only were all of the methods needed to practice the claimed invention well known in the art, but the ordinary artisan has been proven to be fully capable of carrying out the methods of this invention without undue experimentation, as can be seen by the large number of scientific groups who have identified and correlated SNPs of the VKOR gene with warfarin sensitivity. Thus, the Examiner's broad generalizations about the unpredictability of the functionality of polymorphic sites in genomic DNA and her citation of Hacker et al. (which describes a totally unrelated gene polymorphism and totally unrelated phenotype of ulcerative colitis) are not relevant to the present invention. Most importantly, the Examiner fails to take into consideration the applicants' contribution to the art with the identification of the VKOR gene, examples showing identification of marker and non-marker SNPs and applicants' teaching of methods to determine marker SNPs, correlate them with warfarin sensitivity and identify at-risk subjects.

Furthermore, the Examiner's comment that not all SNPs would be predictive of warfarin sensitivity based on the finding that a given SNP was found in a single subject with warfarin sensitivity fails to demonstrate a lack of enablement of the present invention. As applicants have amply demonstrated, one of ordinary skill in the art was adequately armed, at the time of this invention, to carry out the claimed methods without undue experimentation. Moreover, even if there are inoperative embodiments, it is well established that the presence of inoperative embodiments within the scope of a claim does not necessarily render the claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art; i.e., without undue experimentation. *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.* 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984). It is readily apparent, from the discussion and evidence provided herein, that one of ordinary skill in the art could and did carry out the methods of the present invention and identify SNPs of the VKOR gene that are

correlated with increased warfarin sensitivity, as well as identify SNPs in the VKOR gene that are not correlated with increased warfarin sensitivity with expenditure of no more effort than is normally required in the art.

Thus, for at least the reasons set forth above, it is the applicants' view that these factors weigh in favor of enablement of the claimed invention.

The next *Wands* factor analyzed by the Examiner is the level of skill in the art, which the Examiner states is deemed to be high. The applicants concur with this assessment and further point out that the level of skill would be deemed to be quite high, especially in view of the added teachings provided in the applicants' disclosure, establishing that it would be well within the realm of capabilities and knowledge of one of ordinary skill in the present art to carry out the methods of the present invention with nothing more than routine experimentation. Thus, this factor clearly weighs in favor of the applicants.

Finally, the Office Action provides an analysis of the present invention pursuant to the *Wands* factor regarding the quantity of experimentation necessary to carry out the claimed invention. Specifically, the Action states that to practice the invention as broadly as it is claimed, the skilled artisan would have to perform a large study of cases and controls in different human populations to determine whether the C at position 2581 of SEQ ID NO:11 was predictably associated with warfarin sensitivity as well as characterize additional sequences within the VKORC1 gene and determine if they are predictably associated with warfarin sensitivity, as well as determining whether the polymorphisms are so associated in any population or whether the association is population specific. Presumably, it is the Examiner's conclusion that such experimentation would be replete with trial and error experimentation, with the results of each analysis being unpredictable, and that such experimentation is considered undue.

Applicants respectfully point out that in an analysis of whether the claimed invention is enabled, the quantity of experimentation needed to be performed by one of skill in the art is only

one factor to be considered and should be considered in the appropriate context of what would be considered undue, even if extensive. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 152 (CCPA 1977). Furthermore, "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d at 737 (citing *In re Angstadt*, 537 F.2d 489, 502-504, 190 USPQ 214, 218 (CCPA 1976).

In the present invention, as the applicants have noted above, all of the methods needed to carry out the claimed invention were known at the time of this invention and the level of skill of those in this art is quite high. Furthermore, not only does the specification as filed provide more than ample guidance to carry out the methods of this invention, the specification includes an actual reduction to practice of the claimed invention. The methods provided in the present specification as well as those available in the art at the time of this invention are straightforward and routine and there is no evidence to support a statement that identifying a subject's sensitivity to warfarin, identifying SNPs in the VKOR gene of the subject and correlating the presence of a SNP in the VKOR gene with the subject's warfarin sensitivity would "...be replete with trial and error experimentation." Thus, the performance of "a large study of cases and controls in different human populations" to identify the SNPs of this invention would not only be considered by one of skill in the art to be routine in theory; it has also been demonstrated to be routine in practice, as readily evidenced by the large number of studies that have been published that specifically describe carrying out the methods of this invention using routine procedures. Thus, the only conclusion to be drawn from such evidence is that any experimentation associated with the methods of this invention is routine and certainly not undue.

In conclusion, applicants respectfully point out that in a determination of whether the enablement requirement is satisfied, the Examiner must consider all the evidence related to each of the above eight factors and any conclusion of non-enablement must be based on the evidence as a

whole. *In re Wands*, at 737, 740, 8 USPQ2d, at 1404, 1407. For the present invention, when the evidence as a whole is considered, it is apparent that the methods of the claimed invention do not require undue experimentation, and thus claims 1-5 satisfy the requirement for enablement. Applicants therefore respectfully request that this rejection be withdrawn.

III. Rejection under 35 U.S.C. § 112, first paragraph (written description)

The Office Action states that claims 1 and 3-5 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

Applicants respectfully traverse this rejection on the basis that the specification as filed provides adequate written support for claims 1 and 3-5. In particular, it is well documented that for a written description analysis, "[t]he fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." (*Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶1, "Written Description" Requirement,* Federal Register 66, p. 1105 column 2 (Jan. 5, 2001) (hereinafter, "Written Description Guidelines"). Furthermore, for original claims, "[t]here is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." (Written Description Guidelines, p. 1105, column 1). In addition, the Written Description Guidelines establish that for original claims, "[p]ossession may be shown in many ways. For example, possession may be shown, *inter alia*, by describing an actual reduction to practice of the claimed invention." (Written Description Guidelines, p. 1105, column 3).

In the present invention, claim 1 is an original claim and as such finds verbatim support in the specification as filed (see, e.g., page 2, lines 27-32; page 14, lines 20-25; original claim 1). The amendments to claim 1 as provided in the present response are also supported in the specification as filed (e.g., on page 15, lines 8-12). Thus, applicants are entitled to the strong presumption that an adequate written description of the claimed invention was present when the application was filed.

In addition, applicants have described an actual reduction to practice of the claimed invention. The specification provides a specific example of the method of claim 1 in the Examples section on pages 19-22, wherein protocols are described in which subjects were evaluated for their sensitivity to warfarin, DNA samples from the subjects were sequenced for the presence of known single nucleotide polymorphisms (SNPs) and statistical analyses were carried out to identify SNPs associated with increased or decreased sensitivity to warfarin. Those subjects carrying SNPs correlated with increased sensitivity to warfarin were thus identified. An example of a SNP correlated with increased sensitivity to warfarin is set forth in claim 2, which applicants note is not subject to the present written description rejection. Thus, the Examiner acknowledges an adequate reduction to practice of the present invention, in compliance with the written description requirements.

Applicants note that in the Office Action it is stated that the claims encompass a large genus of single nucleotide variants, including deletions, substitutions, and insertions at any site within the VKORC1 gene and that such a genus includes a large number of polymorphisms and mutations for which no adequate written description is provided in the specification. Applicants respectfully point out that claim 1 is not directed to a genus of nucleotide variants; rather claim 1 provides a method of identifying a subject having an increased sensitivity to warfarin by detecting in the subject a SNP in the VKOR gene correlated with increased sensitivity to warfarin. Thus, claim 1 is directed to a method and not to any particular nucleotide variant. As noted above, the method of claim 1 is supported verbatim in the disclosure of the specification and applicants have provided an actual reduction to practice of the method of claim 1. Thus, pursuant to the Written Description Guidelines, applicants have more than adequately demonstrated with reasonable clarity to those of skill in the art that applicants were in possession of the invention as claimed.

To further emphasize the applicants' position, the Examiner's attention is drawn to Example 18 on page 65 of the Revised Interim Written Description Guidelines Training Materials, entitled "Process claim where the novelty is in the method steps." In Example 18, the following claim is set forth:

1. A method of producing a protein of interest comprising;

obtaining *Neurospora crassa* mitochondria,

transforming said mitochondria with a expression vector comprising a nucleic acid that encodes said protein of interest,

expressing said protein in said mitochondria, and

recovering said protein of interest.

In the subsequent analysis of this claim, the Training Materials state that a review of the specification reveals that *Neurospora crassa* mitochondrial gene expression is essential to the function/operation of the claimed invention and that a particular nucleic acid is not essential to the claimed invention. (Emphasis added). The analysis continues on by stating that a search of the prior art reveals that the claimed method of expression in *Neurospora crassa* is novel and unobvious and that the claim is drawn to a genus, i.e., any of a variety of methods that can be used for expressing protein in the mitochondria. The analysis further states that there is actual reduction to practice of a single embodiment, i.e., the expression of β-galactosidase and that the art indicates that there is no substantial variation within the genus because there are a limited number of ways to practice the process steps of the claimed invention. It is concluded in the Training Materials that the claimed invention is adequately described pursuant to the discussion that the single embodiment is representative of the genus based on the disclosure of *Neurospora crassa* mitochondria as a gene expression system, considered along with the level of skill and knowledge in the gene expression art and that therefore one of skill in the art would recognize that applicant was in possession of all of the various expression methods necessary to practice the claimed invention.

A similar analysis, leading to the same conclusion can be applied to the method of claim 1. In the present case, a review of the specification reveals that the detection in a human subject of a SNP correlated with increased sensitivity to warfarin is essential to the function/operation of the claimed invention and that a particular SNP is not essential to the claimed invention. In addition, pursuant to applicants' comments herein regarding the cited art references and how the present invention is distinguished therefrom, it can be concluded that the claimed method of detection in a

human subject of a SNP correlated with increased sensitivity to warfarin s novel and unobvious.

Continuing on with each additional aspect of the above-referenced analysis as set forth in the Training Materials, the claim is drawn to a genus, i.e., any of a variety of methods that can be used to detect a SNP in nucleic acid of a human subject and there is actual reduction to practice of a single embodiment, i.e., the detection in human subjects of the SNP identified in claim 2, which is a SNP correlated with increased sensitivity to warfarin in a human subject. Furthermore, it can be reasonably concluded that a review of the art would indicate that there is no substantial variation within the genus because there are a limited number of ways to practice the process steps of the claimed invention.

Thus, applying the same reasoning to the present invention as applied in Example 18, the described embodiments are representative of the genus based on the disclosure of detection of SNPs correlated with increased sensitivity to warfarin as a way to identify a human subject having an increased sensitivity to warfarin, considered along with the level of skill and knowledge in the art of nucleic acid sequencing, SNP identification and statistical correlation of genotypic markers with phenotypic traits. Thus, one of skill would indeed recognize that applicants were in possession of all of the various methods necessary to practice the claimed invention and that the claimed invention is adequately described.

Claims 3, 4 and 5 as set forth above, provide various aspects of identifying a human subject having increased sensitivity to warfarin (claim 3); identifying a SNP in the VKOR gene correlated with increased sensitivity to warfarin in a human subject (claim 4) and correlating a SNP in the VKOR gene of a human subject with increased sensitivity (claim 5). As noted above for claim 1, all of the claims are disclosed verbatim in the specification (see, e.g., page 15, line 24 through page 16, line 13) and in the original claims and an actual reduction to practice of the methods of each of these claims is provided in the Examples section of the specification as filed. Finally, the same analysis of claim 1 pursuant to Example 18 of the Training Materials is applicable to the methods of claims 3-5 and therefore it is apparent that these claims are also adequately described pursuant to the

written description requirement. Thus, for at least these reasons, applicants believe the present rejection to be overcome and its withdrawal is respectfully requested.

IV. Rejection under 35 U.S.C. § 102(e)

The Office Action states that claims 1 and 3-5 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Oldenberg et al. (US Pregrant publication 2005/0271644). Specifically, the Office Action states that Oldenberg et al. teaches a method of determining polymorphisms in the VKORC1 gene associated with warfarin sensitivity. The Office Action further states that, with regard to claims 1 and 3, although Oldenberg et al. teaches specific mutations in subjects with warfarin resistance, the term "increased sensitivity to warfarin" is a relative term and depends on the comparison and that Oldenberg et al. discloses that individuals with a C at position 292 are more sensitive to warfarin than individuals with a T. The Office Action goes on to state that, with regard to claims 4 and 5, Oldenberg et al. teaches identifying sensitive rats, detecting nucleotide polymorphisms in the subject and correlating the presence of the polymorphism with warfarin sensitivity.

Applicants respectfully traverse this rejection. In particular, claim 1 as recited herein provides a method of identifying a human subject having an increased sensitivity to warfarin, wherein a therapeutic dose of warfarin for the subject is lower than a therapeutic dose of warfarin for a normal subject, comprising detecting in the subject the presence of a single nucleotide polymorphism in the VKOR gene, wherein the single nucleotide polymorphism is correlated with increased sensitivity to warfarin, thereby identifying the subject having increased sensitivity to warfarin. As discussed during the September 25, 2007 interview, Oldenberg et al. does not teach a method of identifying a human subject having an increased sensitivity to warfarin, wherein a therapeutic dose of warfarin for the subject is lower than a therapeutic dose of warfarin for a normal subject, as set forth in pending claim 1. Thus claim 1 is not anticipated by Oldenberg et al. Therefore, applicants believe the present rejection of claim 1 to be overcome and respectfully request its withdrawal.

Furthermore, claims 4 and 5 as presented herein respectively recite a method of identifying a single nucleotide polymorphism in the VKOR gene correlated with increased sensitivity to warfarin, comprising: a) identifying a human subject having increased sensitivity to warfarin; b) detecting in a population of the subjects of (a) above the presence of a single nucleotide polymorphism in the VKOR gene; and c) correlating the presence of the single nucleotide polymorphism of step (b) with the increased sensitivity to warfarin in the population of subjects, thereby identifying a single nucleotide polymorphism in the VKOR gene correlated with increased sensitivity to warfarin (claim 4), and a method of correlating a single nucleotide polymorphism in the VKOR gene of a human subject with increased sensitivity to warfarin, comprising: a) identifying a subject having increased sensitivity to warfarin; b) determining the nucleotide sequence of the VKOR gene in population of the subjects of (a); c) comparing the nucleotide sequence of step (b) with the wild type nucleotide sequence of the VKOR gene; d) detecting a single nucleotide polymorphism in the nucleotide sequence of (b); and e) correlating the single nucleotide polymorphism of (d) with increased sensitivity to warfarin in the subject of (a).

As also discussed during the September 25, 2007 interview, Oldenberg et al. does not teach a method of identifying a single nucleotide polymorphism in the VKOR gene correlated with increased sensitivity to warfarin, comprising identifying a human subject having increased sensitivity to warfarin, nor does Oldenberg et al. teach a method of correlating a single nucleotide polymorphism in the VKOR gene of a human subject with increased sensitivity to warfarin. Thus, the methods of claims 4 and 5 as presented herein are not anticipated by Oldenberg et al. Therefore, applicants believe the present rejection of claims 4 and 5 to be overcome and respectfully request its withdrawal.

V. Rejection under 35 U.S.C. § 102(a)

The Office Action states that claims 1 and 3-5 are rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Rost et al. Specifically, the Office Action states that Rost et al. teaches a method of determining polymorphisms n the VKORC1 gene associated with warfarin sensitivity. The Office Action further states that, with regard to claims 1 and 3, although Oldenberg et al.

teaches specific mutations in subjects with warfarin resistance, the term "increased sensitivity to warfarin" is a relative term and depends on the comparison and that Oldenberg et al. discloses that individuals with a C at position 292 are more sensitive to warfarin than individuals with a T. The Office Action goes on to state that, with regard to claims 4 and 5, Oldenberg et al. teaches identifying sensitive rats, detecting nucleotide polymorphisms in the subject and correlating the presence of the polymorphism with warfarin sensitivity.

Applicants respectfully traverse this rejection. Specifically, as discussed during the September 25, 2007 interview, Rost et al. does not teach the methods of claims 1, 4 or 5 as presented herein and thus Rost et al. does not anticipate these claims. Therefore, applicants respectfully request the withdrawal of this rejection.

VI. New claim 17

New claim 17 as presented herein recites a method of screening for a single nucleotide polymorphism in the VKOR gene of a human subject that is associated with increased sensitivity to warfarin, comprising: a) detecting single nucleotide polymorphisms in the VKOR gene of a human subject; b) performing a population based study to detect the polymorphisms in a group of human subjects with increased sensitivity to warfarin and ethnically matched controls; c) identifying an allele of a single nucleotide polymorphism in the VKOR gene that is associated with increased sensitivity to warfarin. Support for this new claim is provided in the specification as noted above and thus, this claim is adequately supported under the written description requirement. This new claim is added herein pursuant to the Examiner's statement on page 3 of the Office Action that applicant's disclosure and the available art render the method of claim 17 enabled and that therefore such a claim would be patentable. As set forth herein, this claim, as well as pending claims 1-5 are free of the cited art and thus, new claim 17 is believed to be in condition for allowance, which action is respectfully requested.

Having addressed all of the issues raised in the present Office Action, the applicants respectfully submit that all of the claims of this application are in condition for allowance, which

action is respectfully requested. The Examiner is encouraged to contact the undersigned directly if such contact will expedite the allowance of the pending claims to issue. As noted above, should the Examiner fail to find the subject matter of the claimed invention allowable, the applicants respectfully request a telephone interview with the Examiner and her supervisor before the issuance of any further actions.

The Commissioner is authorized to charge Deposit Account No. 50-0220 in the amount of $1230.00 ($1050.00 as the fee for a three month extension of time and $180.00 as the fee for a supplemental Information Disclosure Statement). This amount is believed to be correct. However, the Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,

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CERTIFICATION OF TRANSMISSION

I hereby certify that this correspondence is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4) to the U.S. Patent and Trademark Office on November 30, 2007.

Tracy Wallace